Chapter 1

Introduction: Hydrogen Bond in Molecular Crystals

1.1 Introduction

Relying on hydrogen bond along with various other weak but directional intermolecular interactions, functionalized solids can be engineered with desired properties [1–7]. The hydrogen bond is one of the most explored intermolecular interaction types, because of its unique strength, directionality, relative abundance and their ability to influence material properties [8–15]. Scientific areas evolving based on hydrogen bonding are miscellaneous, right from mineralogy, material science, inorganic and organic chemistry, biochemistry, medicinal chemistry to supramolecular chemistry etc. [2,16–18]. It has been the focus of the researcher ever since its discovery. It has a remarkable impact on the molecular structures, activities, and properties on a huge number of chemical systems, ranging from inorganic to biological systems; thus it demands more research [15,19–23]. In 2011, IUPAC recommended the definition of hydrogen bond as "*an attractive interaction between a hydrogen atom from a molecule or molecular fragment X–H in which X is more electronegative than H, and an atom or a group of atoms in the same or a different molecule, in which there is evidence of bond formation*" and it is well accepted by all [24].

Intermolecular forces like hydrogen bonding, π–π interactions, and van der Waals interactions are responsible to bring molecules closer and build a crystalline solid, also termed as supramolecule or supermolecule [2,25–27]. J. M. Lehn introduced the term supramolecular chemistry and defined it as "*Chemistry Beyond the Molecule*"[26,27]. Within the domain of supramolecular chemistry, crystal engineering is an emerging area of research, which deals with the rational design of functional molecular solids using non-covalent interactions [28,29]. In August 1955, Pepinsky, a physicist, introduced the idea "*Crystal Engineering*" at the conference of American Physical Society, held in Mexico City [30]. This idea was further established by Schmidt during the period of 1950-1970, considering the crystal structure engineering for photo dimerization of cinnamic acids in the solid state [31]. One of the pioneers in this field, G. R. Desiraju defined the phrase ''*Crystal Engineering*'' as "*the understanding of intermolecular*

interactions in the context of crystal packing and the utilization of such understanding in the design of new solids with desired physical and chemical properties"[28,32,33]. Designing a new supramolecular system with desired properties will provide us with a better understanding about non-covalent interactions between molecules within the molecular aggregates and it will transform the pharmaceutical industry and medicine by developing new ways of drug administration and new composite biocompatible materials which will serve as implants of the generation. The subject is growing rapidly and nowadays is one of the major research areas, associated with different self-assembly of molecules via using weak intermolecular interactions such as hydrogen bonding, halogen bonding, π–π, and van der Waals interactions, and metal coordination bonding in various chemical systems such as molecular crystals, metal–organic structural design, nanostructures, and coordination polymers [32,33]. The interdisciplinary subject of crystal engineering has overlap with organic chemistry, inorganic chemistry, supramolecular chemistry, X-ray crystallography, materials research, computational chemistry and pharmaceutical chemistry [32].

Indeed, crystal engineering principles are useful for rational design, control, and applications of organic solids [28,29]. Intermolecular interactions are the driving force in the process of formation of a single component or multi-component crystals [34–36]. Among these intermolecular interactions, hydrogen bonding, halogen bonding and π-stacking are the most influential and frequently occurred in organic multi-component crystals [35]. H-bonds are crucial as it is the most directional in nature. The probable hydrogen-bonding interaction sites that exist in the starting materials offer the way for the synthesis of multicomponent crystals. Molecules are assembled via ordered repeating units of non-covalent interaction to form structural motifs in the crystalline lattice, and G. R. Desiraju first introduced the term '*supramolecular synthon'* to define these interaction motifs [37]. Zaworotko sub-classified supramolecular synthons in two categories viz., homosynthon and heterosynthon based on the interacting functional groups [38]. Homosynthon is triggered by H-bonding between identical functionality, whereas heterosynthon arises when H-bonding occurs between two different functional groups.

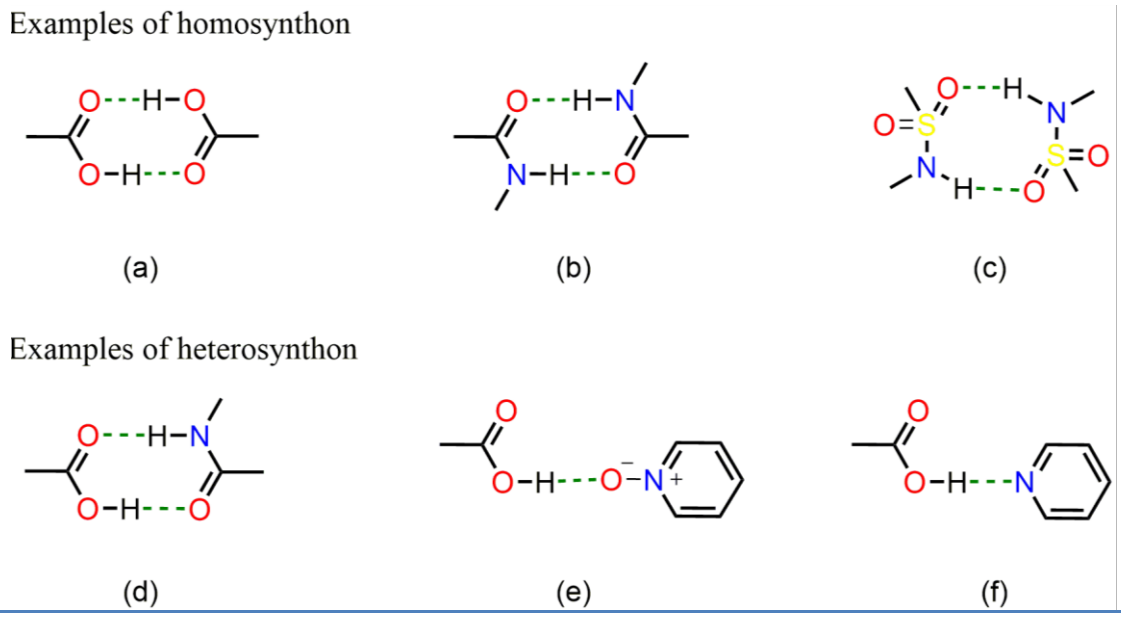


Figure 1.1 Examples of supramolecular synthons, (a) –COOH···COOH homodimer (b) –$CONH_2$···$CONH_2$ homodimer (c) SO_2NH_2···SO_2NH_2 homodimer (d) –COOH···$CONH_2$ heterosynthon (e) –COOH···pyridine-*N*-oxide heterosynthon (f) –COOH···$N_{aromatic}$ heterosynthon.

Etter and co-workers first proposed the hydrogen bond rule which accounts the synthon competition and cooperation in the design and synthesis of cocrystal [39,40]. The rules of thumb to simplify the tactical design of H-bonded entities are also known as hydrogen bond principles. When competing functionalities are available in a particular molecule these rules help to address the issue of lack of understanding of hydrogen bonding synthon probabilities.

They further proposed a graph set notation to describe and analyse different hydrogen bond interaction observed in crystalline solid [41,42]. A general graph-set descriptor is represented as shown below

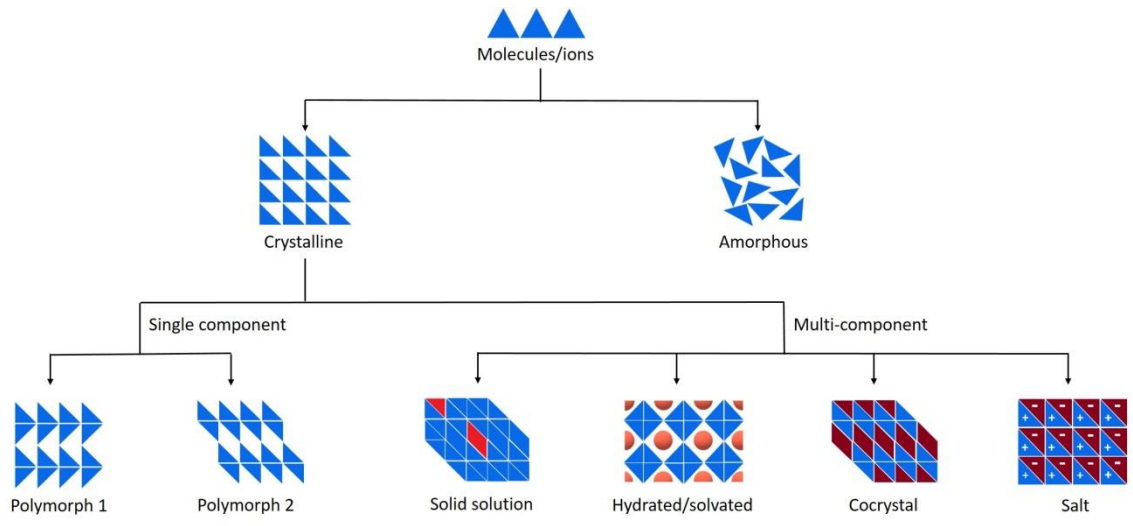
$$G\,{}^{a}_{d}(n)$$

In this notation G represent the descriptor of the hydrogen bonding pattern and is denoted by using one of the following: C=chain, R=ring, D=dimer, S=intramolecular hydrogen bond. The number of acceptors in the hydrogen bond motif is identified by the superscript **a**, and the subscript **d** represent the no the of hydrogen bond donor. The total size of the motif, i.e. the number of atoms involved in the formation of the in the

hydrogen-bonded motif is presented by **n**. Graph set notation is extensively used in the thesis to describe the hydrogen bonding interactions observed in the crystal structures.

1.2 Crystalline Organic Solid Forms

Crystalline or amorphous states are the two broad categories in to which the solid drug forms can be categorized. The crystalline states of a drug molecule are more desirable than amorphous form as many amorphous materials exhibit profound instability and crystalline materials have advantage owing to their easy purification, separation and storage [43,44]. Crystallization of drug molecules can afford different polymorphic forms which can have different crystal packing or molecular conformations [45–47]. Drugs molecules can also crystallize by incorporating other guest molecules in the crystal lattice to generate a multi-component crystal system like hydrates, solvates, salts and cocrystals [1,43,44]. The possible solid forms of drug showing different single and multicomponent crystals have been portrayed in Scheme 1.1. Each of these solid forms can exhibit different physiochemical properties like solubility, dissolution rate, stability, hygroscopicity because of their distinct structural differences. These properties are crucial in drug development perspective as they determine the stability, bioavailability and manufacturing viable dosage form [48,49].



Scheme 1.1 Pictorial representation showing the most probable solid forms that can be adapted by a drug. The multicomponent crystalline solids can also exhibit polymorphism.

1.3 BCS Classification of Drugs

Drugs are generally categorized into four categories on the basis of their solubility and membrane permeability and known as Bio Pharmaceutics Classification System (BCS). In 1995, this unique method of categorisation of drug molecules was introduced by Amidon and co-workers [50]. The categories are BCS class I (high solubility and permeability), class II (low solubility and high permeability), class III (high solubility and low permeability), and class IV (low solubility and permeability) and some examples are depicted in Table 1.1. Introduction of BCS classification has a remarkable impact on sorting out the drug molecules that are associated with poor physiochemical properties for better formulation [51,52]. Nowadays, it has been extensively used by the pharmaceutical industry throughout drug discovery and development processes. According to this classification, about 40% of orally administered drugs that are currently available on the market are reported to exhibit poor aqueous solubility. Among these drugs, 30% is categorized as BCS class II and 10% is categorised in class IV which have extremely low solubility. In addition, aspirant drug molecules in discovery pipelines are also reported to exhibit poor aqueous solubility. Majority of these drugs fall into the BCS class II (70%) and class IV (20%) category.

Table 1.1 BCS classification of drug based on solubility and permeability.

Solubility	**Permeability**	
	High	Low
High	**Class I**	**Class III**
	Example: Theophylline, Metoprolol, Propanolol, Metoprolol, Diltiazem etc.	Example: Acyclovir, enalaprilat, atenolol, ganciclovir
Low	**Class II**	**Class IV**
	Example: Ibuprufen, Ethenzamide, Mefanimic acid, Nisoldipine, Nifedipine etc.	Example: Furosemide, famotidine, ritonavir, paclitaxel

Thus, the poor physiochemical properties of drug molecules demand further attention from researchers to develop a better solid formulation of already existing drug molecules considering the fact that discovery of new drug is a time consuming and staggeringly difficult task. The subject crystal engineering provides a wide range of opportunity for the researchers to engineer various solid-state drug formulations with tuned properties

[53]. These formulations can display tailored biopharmaceutical properties particularly with regard to solubility, processability and to some extent permeability and thereby overall bioavailability. The important role of various solid state forms such as polymorphs, salts, solvates and cocrystals in the pharmaceutical industry is of current research focus and discussed in subsequent chapters of the thesis.

1.4 Pharmaceutical Cocrystal

In pharmaceutical development, the property modulation of active pharmaceutical ingredients (API) has immense significance, as most of the drug molecules carry shortcomings like poor solubility & dissolution, hygroscopicity, low chemical stability etc. The therapeutic ability of a drug depends on its physiochemical properties which are directly correlated with the structure. Poor physiochemical properties of some API demand new approaches to design pharmaceutics with improved physiochemical properties. In recent times the approach, "pharmaceutical cocrystallization" is attaining tremendous attention in the pharmaceutical industry to amend the properties of already existing drug molecules [34,38,54–61].

1.4.1 *Pharmaceutical Cocrystal definition*

Zaworotko and Almarsson first introduced the term pharmaceutical cocrystal in 2004 [38]. A pharmaceutical cocrystal can simply be defined as a crystal assembly, in which at least one of the molecular components is an API that binds with another target molecule (coformer) via different intermolecular interactions. Recently, FDA reviews the previous April 2013 guidelines about cocrystal for the industry, "Regulatory Classification of Pharmaceutical Co-Crystals", which defines cocrystals as a drug product intermediate. The recent guideline acts as a boon for cocrystal research. FDA proposed the following definition in the draft guidance: "*Solids that are crystalline materials composed of two or more molecules in the same crystal lattice*" [62]. Additionally, to acquire product approval the following conditions must be satisfied

(i) Evidence must be provided to prove that the unit cell comprises both the API and coformers
(ii) In a physiological medium, the cocrystal must dissociate before reaching the pharmacologically active site

(iii) The cocrystal must follow the ΔpK_a rule i.e. (pK_a (base)-pK_a (acid)) < 1, ensuring neither proton transfer nor the formation of salt.

European Medicine Agency (EMA) similarly published a reflection paper defining pharmaceutical cocrystal as a "*homogenous (single phase) crystalline structures made up of two or more components in a definite stoichiometric ratio where the arrangement in the crystal lattice is not based on ionic bonds (as with salts)*" [63]. Additionally, this guideline stresses on the selection of appropriate non-hazardous conformer/ excipient. If cocrystal consists of more than one therapeutic molecule than it must be considered as fixed-dose combination and the starting materials ratio must be indicated clearly.

The supramolecular synthon approach provides strategic insights in designing and synthesis of new cocrystal [29,37]. Based on this approach, it is possible to find out APIs and coformers which exhibit complementary hydrogen bonding sites. Understanding the sustainable interaction that guides the crystal packing is in a nascent stage in crystal engineering, which needs to be explored further. The availability of H-bond donor and acceptor site in the coformers and API selected for cocrystal synthesis is a must. Thus, the selection of suitable and well-matched coformer is the most critical stage of cocrystal designing for a particular drug molecule. Designing of cocrystal involves different stages, viz., (1) Examining the structure of the targeted API molecule to identify the potential functional groups for viable molecular interactions (2) Analysis of different supramolecular synthons (3) Finding out appropriate coformers.

1.4.2 Coformer Selection

In pharmaceutical cocrystal formulation, the coformer must be non-toxic and pharmaceutically acceptable. Generally, they are picked from the GRAS (generally regarded as safe) list prepared by the USA Food and Drug Administration (FDA) which contains more than 3000 substances. Food additives, preservatives, drug excipients, vitamins, bio-molecules are the most commonly used coformers [60,61,64]. Proper selection of coformer has utmost significance in cocrystal design and synthesis. Though supramolecular synthon approach is frequently used to predict and design cocrystals, however, it is quite complicated to predict the synthon precisely for molecules which contain several functional groups. In this respect, analysis of the Cambridge Structural Database (CSD) and understanding of crystal engineering principles are important [65].

CSD is a repository of crystal data and useful tool to study possible H-bonding and other intermolecular interactions, which is helpful in designing of various expected synthon. It is the most useful tool to identify the possible coformers for an API, based on viable interaction sites. Hydrogen bond propensity calculations tool developed by Cambridge Crystallographic Data Centre (CCDC) is emerging as an effective means to predict and design of cocrystal based on the statistical analysis of intermolecular interactions, for example, hydrogen bonds in the relevant structures [66,67]. This approach, also known as Fabian's method, can be exploited for coformers screening for a particular API [68]. Relying on this method it is possible to identify the coformer which exhibits the higher propensity of stronger intermolecular interactions. Accordingly, these coformers are chosen for cocrystallization. Jones et al. applied this tool to predict the coformer selection of anti-malarial drug pyrimethamine considering different aliphatic carboxylic acid coformers and compared the findings with the experimental results [69].

Hunter and co-workers established a virtual cocrystal screening technique, which forecasts the prospect of cocrystallization depending on the calculated molecular electrostatic potential surfaces in the gas phase [70]. There are several other approaches such as lattice energy calculations; software-based design such as conductor-like screening model for real solvents (COSMO-RS) which are proved to be helpful in the design and synthesis of cocrystal. Steed et al. showed from exhaustive CSD screening that molecules crystallizing with Z'>1 are more prone to cocrystallization than molecules with Z'=1 [71]. This signifies that compounds which crystallize with more than one molecule in the asymmetric unit in their pure form are likely to be a good candidate for cocrystal formation because they are, in general, have lesser complementary binding sites, size and shape than compounds with one molecule in the asymmetric unit in their pure state.

1.4.3 Salt vs. Cocrystal

Among multi-component crystalline system salts and cocrystals can be differentiated by the position of the proton between an acid and a base interaction sites. Proton transfer is observed for salt; but not in cocrystals. The proton transfer is predictable based on the ΔpK_a rule [72,73]. Often, coformers are selected considering the pK_a rule. ΔpK_a between coformer and API governs the formation of salt or cocrystal. It is well accepted that an

acid-base adduct has the highest propensity to produce salt if the pK_a difference between them is greater than 3.75. Likewise, a neutral cocrystal can be expected when the ΔpK_a <0. Adducts are expected to have a mixed ionization state when ΔpK_a falls in the range 0 and 3.75 as shown in Figure 1.2.

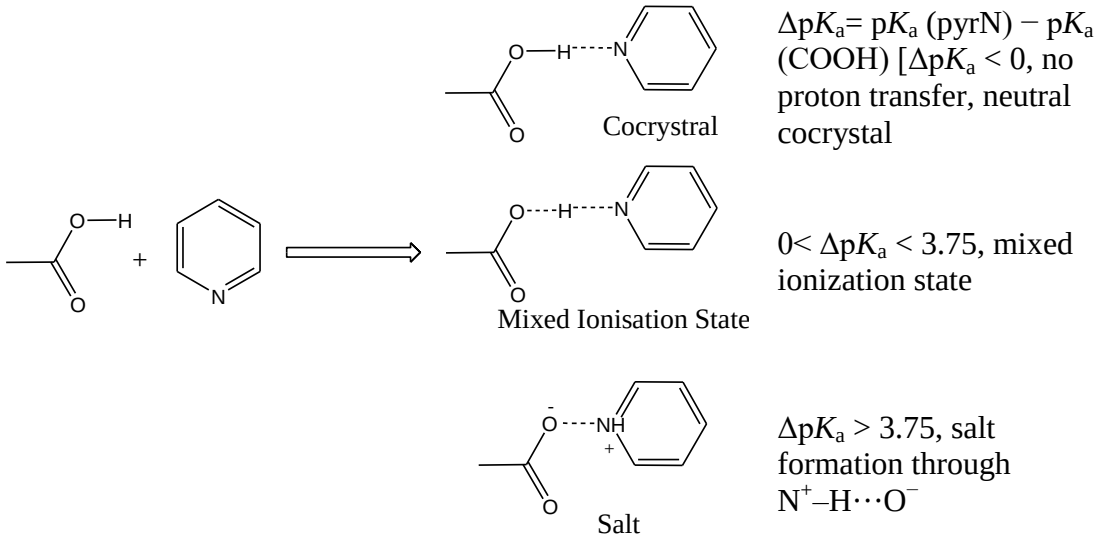


Figure 1.2 Representation of the pK_a rule to predict the possibility of proton transfer in a multicomponent system. This Scheme is reproduced from the PhD thesis entitled '*Structural and Thermal Analysis of Organic Solids'* by B. Sarma, 2009, University of Hyderabad, India.

By performing an extensive CSD analysis for 6465 crystalline complexes covering both ionised and non-ionised acid-base pairs, Aura established a linear relationship between ΔpK_a and the degree of proton transfer. The results are in a good agreement with the pK_a rule, while ΔpK_a falls between −1 and +4 [74].

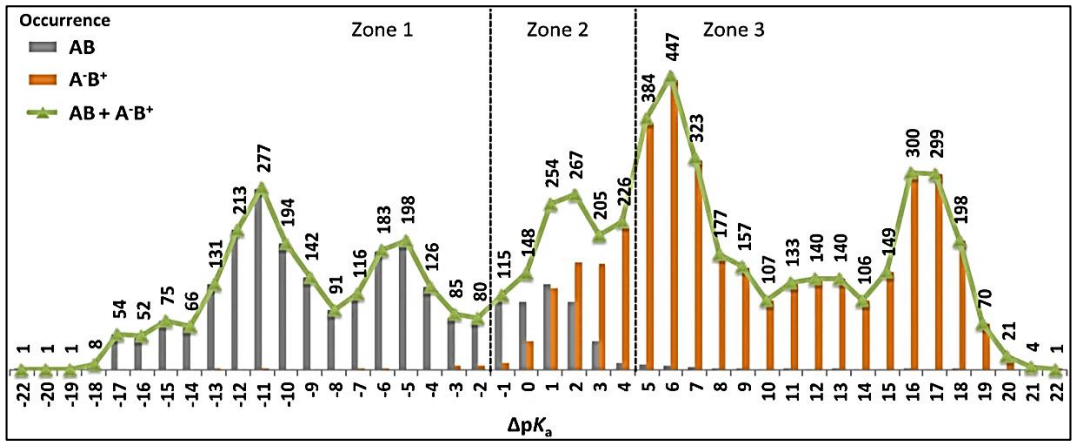


Figure 1.3 Calculated existence of neutral AB (grey) and ionic A^-B^+ (orange) as a function of the calculated ΔpK_a manifested from a CSD study of 6465 acid-base complexes [74].

1.4.4 Synthesis of Cocrystal

Because of its potential advantages in drug formulations, cocrystal is receiving widespread recognition in the field of drug development. Nowadays, in pharmaceutical industries, cocrystal screening is becoming a routine exercise. Till date, various methods have been applied for the synthesis of cocrystals [75,76]. Based on the use of solvents, the cocrystal synthesis methods can be broadly divided into two categories, solid-state and solution-based methods.

Solution based method: The most widely prevailing method for cocrystal synthesis involves the solution crystallization using common laboratory solvents. A stoichiometric amount of drug molecules and the coformer/excipients chosen from GRAS list are dissolved in the solvents and kept for slow evaporation at ambient conditions. The wide range of experimental conditions during solution crystallization may improve the chances of identifying new cocrystals. For example, cocrystallization experiments can be conducted from solvents of different polarities and solvent mixtures. The rate of evaporation of the solvent can also be varied by changing the experimental temperature. The solvent selection is of great importance for cocrystallization, with the possibility of incorporation of the solvent molecule in the lattice site to maintain the hydrogen bond donor-acceptor ratios. Other synthetic techniques include slurry mediated experiment, ultrasonic assisted solution crystallization, seeding, supercritical fluid crystallization, sono-crystallization, and spray drying etc. [77–81].

Solid based method: Solid state reactions are the most readily used process for cocrystal synthesis as they are advantageous. Particularly it is considered a green approach for cocrystals synthesis because of the lack of use of organic solvents or minimum use of organic solvents. Moreover, in most cases, it provides excellent purity and quality, the high yield and the fast processing times. Mechanochemical grinding is one of the most commonly used methods for the preparation of cocrystals at lab-scale [82,83]. It has advantages not only because of green chemistry but in most cases it generates pure cocrystals. Other solid-based methods include hot-melt extrusion, twin-screw extrusion, and extrusion matrix-assisted cocrystallization etc. [76,81,84].

Despite their promising development, the application of cocrystals in the pharmaceutical industry is still limited due to the lack of a suitable method for large scale production [81]. Thus, it is essential to develop a scale-up crystallization process for industrialized

use. Gagnière et al. developed a slurry-based crystallization technique for the scale-up of carbamazepine nicotinamide cocrystals based on the prior understanding about the phase solubility of cocrystal components [85]. However, most of the slurry methods are non-stoichiometric and needs extensive command over thermodynamic and kinetic factors to produce uncontaminated cocrystal material. Paradkar et al. demonstrated solvent free continuous cocrystallization (SFCC) as an effective technique in controlling the stoichiometry of caffeine and maleic acid 1:1 and 2:1 different stoichiometry cocrystal [86]. The 2:1 cocrystal is unstable at room temperature. So, it is challenging to stabilize and obtain phase pure 2:1 stoichiometry. However, 2:1 stoichiometry has been attained by SFCC with temperature control and 2:1 cocrystal doesn't convert to 1:1 using this technique. However, it is possible to covert 1:1 cocrystal to 2:1 stoichiometry using this technique. This work implies that through controlling the ratio and process conditions such as extrusion temperature it is possible to control stoichiometry in cocrystal.

Jayasankar et al. demonstrated an interesting study on how moisture uptake can generate cocrystals of carbamazepine with saccharin and nicotinamide [87]. They have carried out a similar experiment for cocrystal of theophylline or caffeine with dicarboxylic acid coformers. By analysing of process formation of cocrystal via microscopy they established a mechanism of cocrystal formation in presence of moisture at deliquescent conditions. They proposed that the cocrystals formation involves three stages, viz. (1) moisture uptake, (2) dissolution of reactants, and (3) cocrystal nucleation and growth as depicted in Figure 1.4.

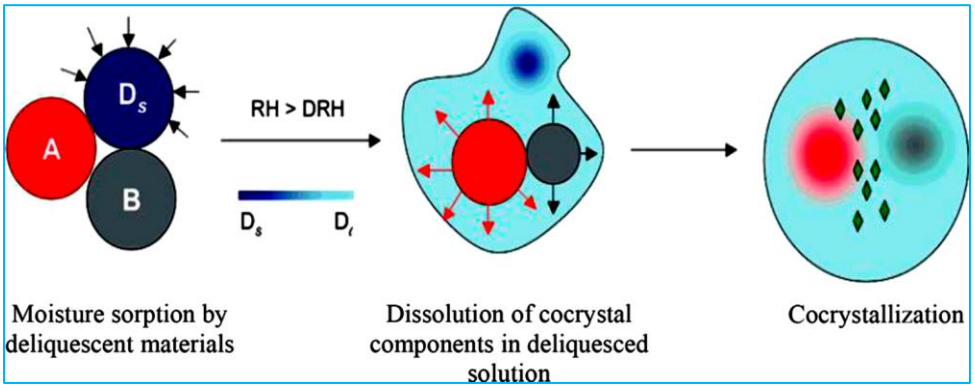


Figure 1.4 Proposed mechanisms showing the moisture uptake route leading to deliquescence, reactant dissolution, and cocrystal formation. A and B are cocrystal formers, D_s represents solid deliquescent additive, and D_l is the solution phase generated by deliquescence at RH greater than deliquescence RH [87].

1.4.5 Cocrystal Characterization

The most common techniques used for the characterization of novel cocrystals forms include powder X-ray diffraction (PXRD), single-crystal X-ray diffraction (SCXRD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), infrared and Raman spectroscopies and solid-state nuclear magnetic resonance (ssNMR) [60,61]. Apart from different analytical techniques, computational software such as Crystal explorer is nowadays extensively used to analyse Hirshfeld surfaces, calculate different molecular interaction contribution etc. [88].

X-ray diffraction technique: SCXRD is a routinely used method to confirm the composition of cocrystal; however, producing a suitable crystal for is not always possible. In this context, structure elucidation from PXRD patterns of microcrystalline powder samples, based on Rietveld refinement has been proved to be effective. For instance, Lapidus et al. performed a double-blind experiment to demonstrate the efficiency and precision of high-resolution PXRD in structure elucidation of 10 cocrystals [89]. Moreover, PXRD is very helpful in the identification of new cocrystal phases, as PXRD of cocrystals exhibits characteristic sharp peaks that are entirely different from the peaks of the parent molecules.

Thermal techniques: Various thermal methods are also used for characterization and quantification of potential new cocrystals. The thermal analytical techniques such as DSC, TGA provides information about thermal stability, solvent inclusion in crystal lattice, cocrystal purity heat or heat flow, enthalpy, etc. Generally, the cocrystal melting observed by DSC analysis falls mostly between the melting temperatures of the pure parent compounds [56]. DSC is also helpful in differentiating between a cocrystal phase and eutectic mixture [60].

Spectroscopic techniques: Vibrational spectroscopy (FT-IR and Raman) and nuclear magnetic resonance (NMR) are most commonly used spectroscopic techniques for identification of cocrystal [61]. FT-IR spectroscopy is an effective tool in detecting intermolecular H-bonding. Due to the presence of intermolecular H-bonding in cocrystals, it will give an FT-IR spectrum that entirely different from the starting materials. Thus by comparing FT-IR spectra of the cocrystals with individual components FT-IR, it is easy to identify the formation of cocrystal [90]. Moreover, it is possible to detect the proton transfer from –COOH coformer by analysing the FT-IR

spectra and we have discussed it in subsequent Chapter 1. Raman spectroscopy has been used to study the in situ formation of cocrystals. For instance, Rodríguez-Hornedo et al. used fibre optic Raman spectroscopy for in situ monitoring of carbamazepine: nicotinamide cocrystallization in macroscopic scales considering solutions, suspensions, slurries, and wet solid phases [91]. Kojima et al. used Raman spectroscopy to screening cocrystal of indomethacin during high-throughput slurry screening with 45 different coformers and to differentiate between a physical mixture and a cocrystal [92]. NMR spectroscopy is another powerful tool for screening cocrystal. Vogt et al. demonstrated the use of solid-state NMR (ssNMR) technique for characterization of cocrystals by identifying hydrogen bonding and local conformational changes by $^{1}H–^{1}H$, $^{1}H–^{13}C$ and $^{19}F–^{13}C$ coupling [93]. Maruyoshi et al. used 2D ^{1}H double-quantum and $^{14}N–^{1}H$ & $^{1}H–^{13}C$ heteronuclear magic-angle spinning (MAS) NMR to detect the particular intermolecular hydrogen-bonding interactions $COOH\cdots N_{arom}$ and $C–H_{arom}\cdots O=C$ in the cocrystal of indomethacin–nicotinamide [94]. Jones et al. demonstrate the use of another spectroscopic technique Terahertz time-domain-spectroscopy in quantitative monitoring of mechanochemical cocrystal formation of phenazine and mesaconic acid [95]. In an interesting study, Steven et al. demonstrated the use of X-ray photoelectron spectroscopy (XPS) in combination ^{15}N ssNMR to detect of the degree of proton transfer to differentiate among salt and cocrystal of theophylline [96].

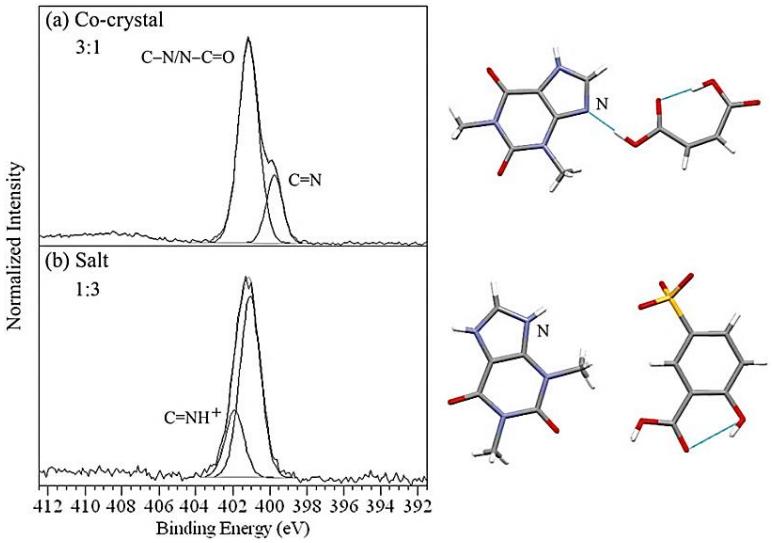
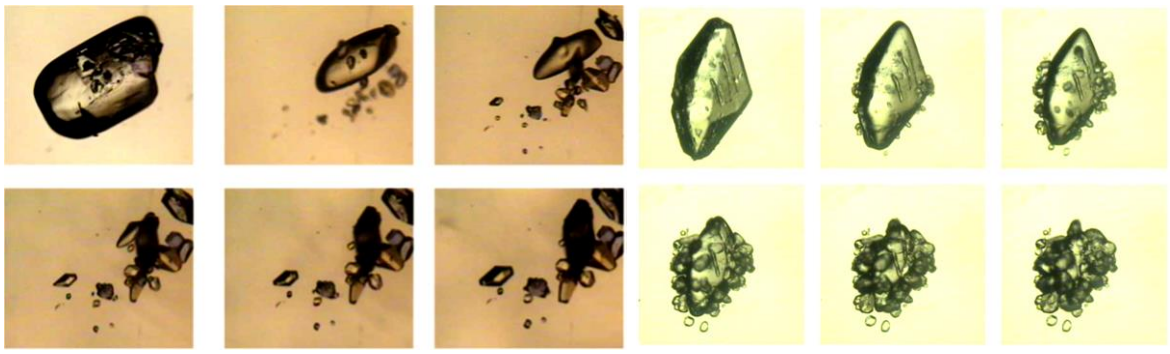


Figure 1.5 N 1s XPS spectra of (a) the theophylline and maleic acid cocrystal and (b) the theophylline/5-sulfosalicylic acid dihydrate salt showing the ratios for types of nitrogen [96].

Microscopy: Optical microscopy is a useful tool to study the crystal habit, phase transition and check the purity of cocrystal phases. Seaton and co-workers demonstrated the use of real-time optical microscopy to examine the solution-mediated phase conversion of 1:1 and 3:2 stoichiometry cocrystals of *p*-toluene sulfonamide and triphenylphosphine oxide [97]. In order to investigate the stability and conversion of the cocrystal, they added one upon the saturated solution of other. The 3:2 cocrystals first dissolute and the remaining crystal behave as crystal seed. In the conversion of 1:1 cocrystal the new crystals are gathering around the dissolving surface of the seed crystal as shown in Figure 1.6.



(a) (b)

Figure 1.6 (a) Solution mediated phase transformation of 3:2 cocrystal in saturated solution of 1:1cocrystal. (b) Transformation of 1:1 cocrystal in saturated solution of 3:2 cocrystal [97].

Hot stage microscopy (HSM) is one of the widely used microscopic techniques in the screening of new pharmaceutical cocrystals formation. It is easy to identify the cocrystal melting of a binary system by HSM. Park et al. performed cocrystal screening of 2-[4-(4-chloro-2-fluorophenoxy)phenyl]pyrimidine-4-carboxamide using HSM considering 26 different carboxylic acids. They used Kofler technique, in which binary are melted next to each other and at the interface, a cocrystal containing both components form under appropriate conditions. Blagden et al. demonstrated the potential of HSM in investigating the cocrystals formation/ screening considering the cocrystals of nicotinamide with seven different APIs [98]. The hot stage images depicted the growth of cocrystal phases during melting. The cocrystals are observed at the interface of the melting of the two components which produces a mixing zone. The particle size and crystal morphology of cocrystals can be analysed by using a scanning electron microscope (SEM) [99]. High-resolution SEM, atomic force microscopy (AFM) can provide the evidence about the surface topography of cocrystal [100].

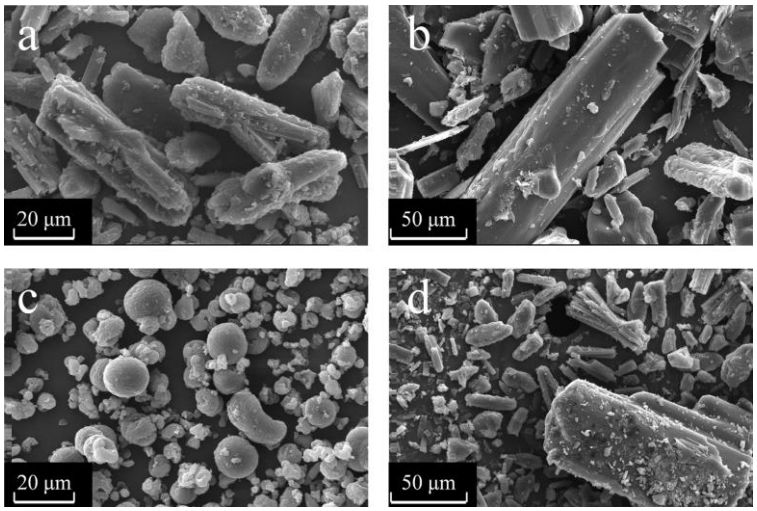


Figure 1.7 SEM images (a) myricetin, (b) proline, (c) myricetin-proline cocrystal and their (d) physical mixture [99].

1.4.6 Stoichiometric Cocrystal, Eutectic Solid or Solid Solution

Occasionally, researchers encounter other multicomponent solid forms of drugs like eutectic mixture and solid solution in the midst of cocrystal synthesis [101]. Cocrystals are different from a eutectic mixture in the sense that the latter can be defined as a blend of two or more components, which are typically, do not interact to produce a new chemical entity. However, at certain ratios, the mixtures inhibit the crystallization of each other and generate a multicomponent system, which has a lower melting point than either of the components. A solid solution is a mixture of solid, in which the crystal lattice of the primary component contains a trivial amount of another component in a homogeneous manner [101].

Designing of cocrystals frequently relies on hydrogen bond donor-acceptor ratios of the starting materials; however, the crystallization outcome may differ depending upon the experimental conditions [83,86]. There are examples where stoichiometry of cocrystal varies irrespective of starting material ratio taken. Como et al. introduced the term stoichiomorphism to define the phenomenon of the appearance of different stoichiometry cocrystal from the same components [102]. Although different stoichiometry of cocrystals is composed of the same components, they are different from the polymorph as they do not signify the metastable forms [58]. This is due to the fact that different polymorphs of a molecule exhibit metastability to the thermodynamic polymorph. The existence of different stoichiometry cocrystal of a particular system facilitates the opportunity to acquire more solid forms of a drug. However, understanding the factors

which govern the formation of different stoichiometry is crucial considering their reproducibility and stability. The possible factors which might be responsible for the formation of different stoichiometry cocrystal can be summarised as follows:

1. Unmatched hydrogen bond donor-acceptor ratio between starting materials.
2. The typical tendency of molecules to attain the highest packing efficiency in crystal and adjustment of crystal symmetry.
3. The competition between various functionality to form supramolecular synthons could lead to frustration in crystal packing thereby producing cocrystal with Z′>1.
4. The existence of multiple supramolecular synthon formation propensities.

There are reports on how a specific solvent selectively produces particular stoichiometry cocrystals. The stability of different stoichiometry cocrystals can be different in a different solvent. Benzoic acid isonicotinamide produces two cocrystals with 1:1 and 2:1 ratio and it has been found that both the cocrystal are stable at different aqueous solution compositions [103]. However, the 1:1 stoichiometry cocrystal is stable and exclusively obtained only from ethanolic solutions. Crystallization from aqueous or methanolic solutions produces both the 2:1 and the 1:1 cocrystal depending on the composition variations. Stoichiometry control is important with respect to the purity of cocrystals. Moreover, the physiochemical properties of drugs may vary with different stoichiometry cocrystals. For instance, there are examples of different stoichiometry cocrystals composing of the same components, which display entirely different properties such as solubility, dissolution, stability etc. [104]. Alike, behaviour has been observed for different stoichiometry cocrystal of theophylline with aminobenzoic acid and is demonstrated in Chapter **3**.

1.4.7 Physiochemical Property Modification

Cocrystal technology is useful, particularly in the pharmaceutical industry, due to its applicability to resolve the issue of poor pharmacokinetic and physiochemical properties that are associated in a drug [56,57,59–61,77]. In general, physiochemical properties include the stability, hygroscopicity and solubility etc. while pharmacokinetic property represents the intrinsic dissolution rate, release and permeation and overall bioavailability of a drug. For an orally administered drug, solubility and permeability are the two key issues that need to be addressed. Devoted research has been in progress to

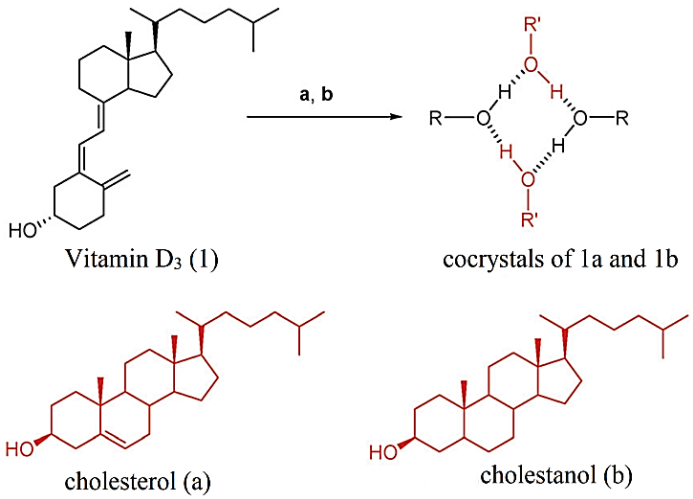
resolve these issues. There are several examples reported in the literature, where cocrystal of such drug emerged as promising means to ameliorate the oral bioavailability of parent drug molecule by modifying its physiochemical and pharmacokinetic properties [61]. The majority of reports in literature explain such modification as an influence of coformer used in cocrystal synthesis. It has been established that coformer with higher aqueous solubility usually generates cocrystals with improved solubility [56]. A number of examples showing the modification of different properties via cocrystallization have been discussed in the subsequent section.

1.4.7.1 Phase stability

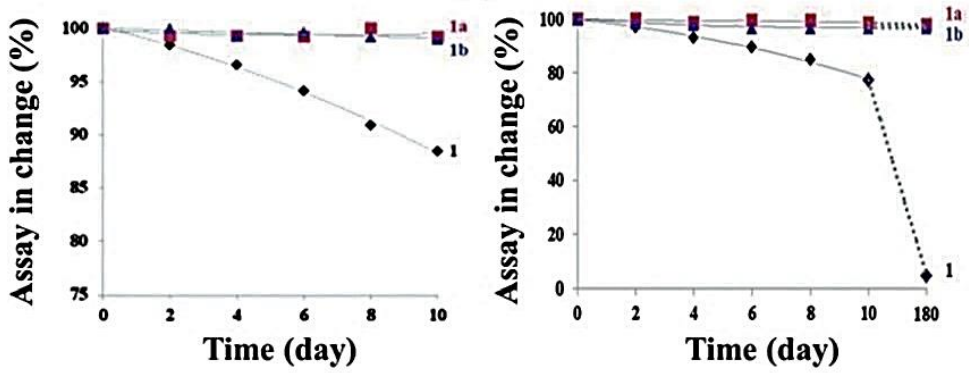
The moisture absorption can lead to a hydrated form of a drug, which may possibly affect the quality and efficacy of it. Also, it is well documented that the moisture absorption results in hydrolysis of many drugs [105]. Moisture sorption can affect adversely release behaviour, life span, storage, handling and transportation drugs. Cocrystal technology is instrumental in avoiding the hydrate formation of drug molecules and thus improving the physical stability of a drug. Caffeine is a central nervous system stimulant and a muscle relaxant but highly hygroscopic at atmospheric condition. Hence, its stability is of concern in the pharmaceutical industries as it can affect the processing, packaging and drug formulation. Pharmaceutical cocrystallization with engineered principles emerged as a remedy of it [54]. The cocrystal of caffeine with oxalic acid via O−H···N and C−H···O hydrogen bonding has been reported to have remarkable stability towards relative humidity up to several weeks with no water molecule intake in the crystal lattice. Similarly, the cocrystals of theophylline with oxalic, malonic, maleic and glutaric acids also display greater stability towards humidity than raw theophylline. Higher stability of the cocrystals attributed to the formation of $R_2^2(7)$ carboxylic acid-imidazole heterosynthons. Cherukuvada et al. reported the hydration stability improvements of drug nitrofurantoin, known for transformation to a hydrate form in an aqueous medium, via cocrystallizing with *p*-aminobenzoic acid. Henck et al. reported the cocrystals of pterostilbene, a nutraceutical compound, with caffeine and carbamazepine having remarkable stability towards temperatures and relative humidity up to 98% and along with enhancement in solubility. There is an enormous number of pharmaceutical cocrystals, for example, niclosamide-caffeine, indomethacin–saccharin, ibuprofen–nicotinamide, flurbiprofen–nicotinamide, which

exhibit added hydration stability compared to the pure APIs [56,106]. Thus, cocrystal technology is an effective tool to prevent hygroscopicity of drug and in this manner improve the overall stability and efficacy. In Chapter 2 we have demonstrated a coformer selection strategy to stabilize theophylline cocrystals.

The hydrolytic degradation of antitumor prodrug temozolomide in aqueous condition was successfully resolved through cocrystallization with succinic acid. This cocrystal demonstrated exceptional stability up to 6 months [107]. Chemical and physical stability enhancement of vitamin D_3 via cocrystallization is reported in 2014 by Mei et al. [108]. Because of the presence of unstable conjugated triene group in vitamin D_3, it undergoes topochemical reactions. Vitamin D_3 can adopt two different stereoisomers depending on the reaction and storage conditions. Because of this instability, the drug is hardly formulated in a solid dosage form. However, the cocrystals of vitamin D_3 with cholesterol and cholestanol are conformationally different and topochemically stable by the formation of O–H···O hydrogen bonds as shown in Figure 1.8. In Chapter 5 we have demonstrated the stability improvement of drug famotidine via cocrystallization approach.



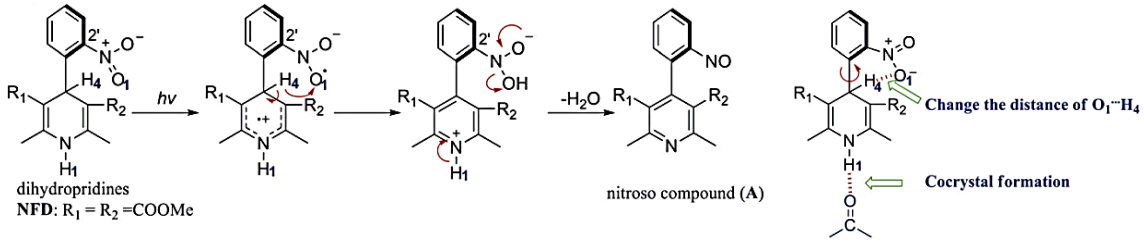
(a)



(b)

Figure 1.8 (a) Four-membered square-shaped H-bonding structure observed in cocrystal of vitamin D_3 (1) and coformers cholesterol and cholestanol; (b) Variations of vitamin D_3 assay upon storage (left) at 23 ºC under illumination of 5000-1 and (right) at 40 ºC /75% RH [108].

A latest report demonstrates the cocrystal of nifedipine with isonicotinamide, which exhibit superior photostability compared to the parent drug nifedipine [109]. The change of molecular conformation and hydrogen bonding interactions is attributed to responsible for amending the photo-stability nifedipine in molecular level.



(a) (b)

Figure 1.9 (a) Photo degradation mechanism of dihydropyridines, e.g. nifedipine (b) Strategy of protecting the two correlative photoreaction sites through cocrystallization [109].

1.4.7.2 Solubility and Dissolution

The improvement of drug solubility by cocrystallization can be explained on the basis of spring and parachute model of drug release [57]. Cocrystals can be considered as a metastable form with respect to a thermodynamic point of view. It has been established that coformer having higher aqueous solubility produces cocrystals with improved solubility [56]. Commonly, the solubility of coformer is several folds higher than the API. Therefore, in the presence of an aqueous environment, the more soluble part of cocrystal, i.e. coformer, slowly comes out into the solution from the crystal lattice,

thereby leaving the drug molecules behind. Thus, due to the faster dissolution of coformer molecules into the solution, the drug particles assembled to form amorphous-like supramolecular aggregates via loose self-aggregation and hydrogen bonding. Nangia et al. proposed that these aggregates of molecules gradually transforms into the lowest energy thermodynamic polymorph through an intermediate metastable polymorphic state by following the Ostwald's law of stages (OLS). Typically, it requires sufficient time, usually a few hours, for the drug to transform through metastable high energy form to the thermodynamic polymorph. This permits the drug to exhibit the ''parachute effect'' and thereby provides an accelerated dissolution. The presence of a higher soluble excipient/ coformer inhibits the drug precipitation and thus acts as a parachute. However, in the absence of a coformer/ excipient, instant precipitation to the stable polymorphic forms happens via the ''spring effect'' which only offers modest solubility.

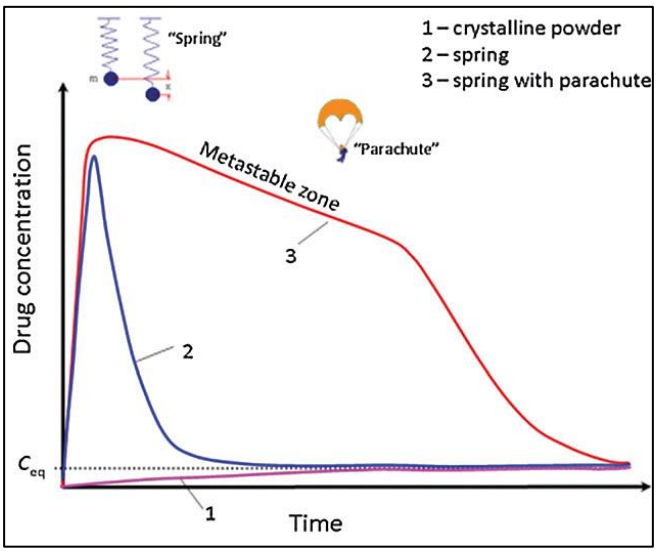
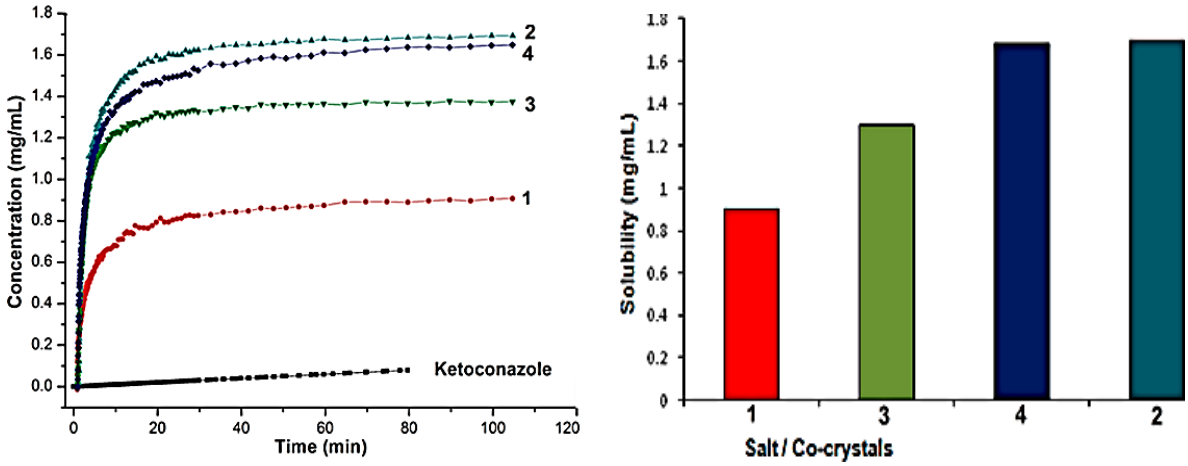


Figure 1.10 The concept of spring and parachute model to concept to attain high apparent solubility of less soluble drugs [57].

The overall bioavailability of a drug is subjected to their biopharmaceutical property that includes the aqueous solubility and permeability. There are more than 100 reports available in the literature about the solubility improvement of drugs via cocrystallization. One of the earliest examples is the improvement of aqueous solubility of itraconazole, an antifungal drug via cocrystallization with L-malic acid L-tartaric acid [110]. Cocrystal observed to have a dissolution rate comparable to that of the marketed amorphous formulation Sporanox (1). Desper et al. demonstrated the aqueous solubility modulation of an anticancer drug hexamethylenebisacetamide via cocrystallization with dicarboxylic

acids [111]. The outcomes display almost 2.5 order magnitude improvement of aqueous solubility for the cocrystal with succinic acid, glutaric acid and adipic acid. However, the cocrystals with diacids having a longer aliphatic chain, show reduced aqueous solubility because of the less polar and more hydrophobic nature of the coformers. Martin et al. report a 100-fold solubility enhancement in water for Ketoconazole cocrystallization with fumaric and adipic acids [112]. Ketoconazole is a BCS class II drug with extremely low solubility. It produces one 1:1 stoichiometry oxalate salt (1) and three cocrystals with fumaric (2), succinic (3), and adipic (4) acids. The cocrystals exhibit better solubility than ketoconazole and its oxalate salt. This result endorsed the fact that, salts are not necessarily more soluble than cocrystals and validate the benefit cocrystallization techniques to enhance the dissolution rate of poorly water-soluble drugs like ketoconazole (Figure 1.11).



(a) (b)

Figure 1.11 (a) Powder dissolution profiles of ketoconazole and ketoconazole oxalate salt (1), cocrystal with fumaric Acid (2), succinic Acid (3), adipic Acid (4) in aqueous condition**;** (b) Comparison of ketoconazole cocrystal solubility with its oxalate salt [112].

For multiple stoichiometry cocrystal as the ratio of more soluble conformer increases, it is expected to favour dissolution. However, cocrystal with highest soluble conformer does not necessarily show higher dissolution [104]. Matzger et al. measured the dissolution and solubility behaviour with respect to conformer concentration considering carbamazepine (CBZ)/*p*-aminobenzoic acid (*p*-ABA) 1:1 and 2:1 and 4:1 cocrystal. They reported that the 4:1 cocrystal is 'schizophilic' i.e. unstable than the starting materials. The higher dissolution of carbamazepine for 4:1 cocrystal in acetonitrile compared to 2:1

cocrystal was attributed to the schizophilic behaviour supported by relatively weak intermolecular interactions in its crystal lattice. The lower dissolution for 2:1 relates to the lower solubility of *p*-ABA in acetonitrile and strong intermolecular interactions present in the crystal structure.

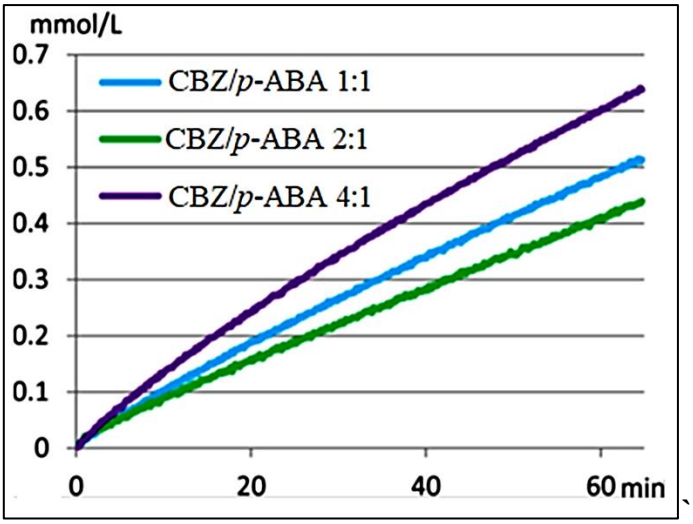


Figure 1.12 Comparison of cocrystal dissolution for different stoichiometry cocrystal of carbamazepine [104].

Apart from improving the solubility and dissolution profile of drug molecules, cocrystallization is instrumental in controlling the release rates of the drug as well [113]. For instance, cocrystallization of ribavirin (RBV) with 3,5-dihydroxybenzoic acid (1), gallic acid (2), and barbituric acid (3) have demonstrated reduced release rate compared to the pure drug in the buffer solution of pH 6.8 as shown in Figure 1.13. RBV is an antiviral drug, but its applicability is limited because of the peak-to-trough fluctuation of drug concentrations in plasma. Chen et al. described this reduced release behaviour of the cocrystal based on the crystal packing. The crystal structures analysis revealed that in cocrystals RBV molecules are tightly trapped in supramolecular organic channel framework or sheet via the formation of multiple hydrogen bonds and as a consequence, the dissolution was reduced.

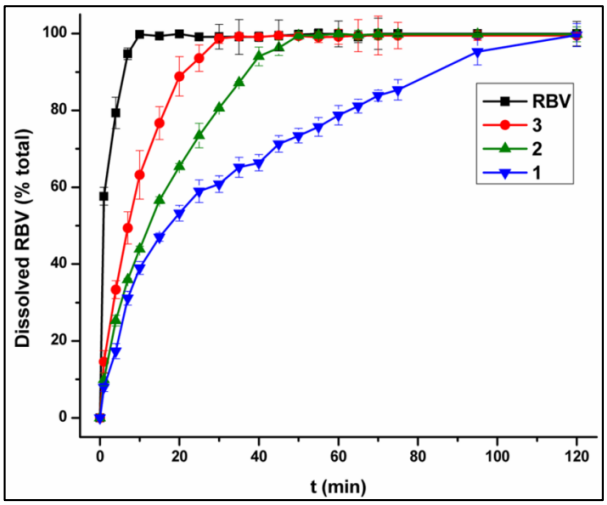
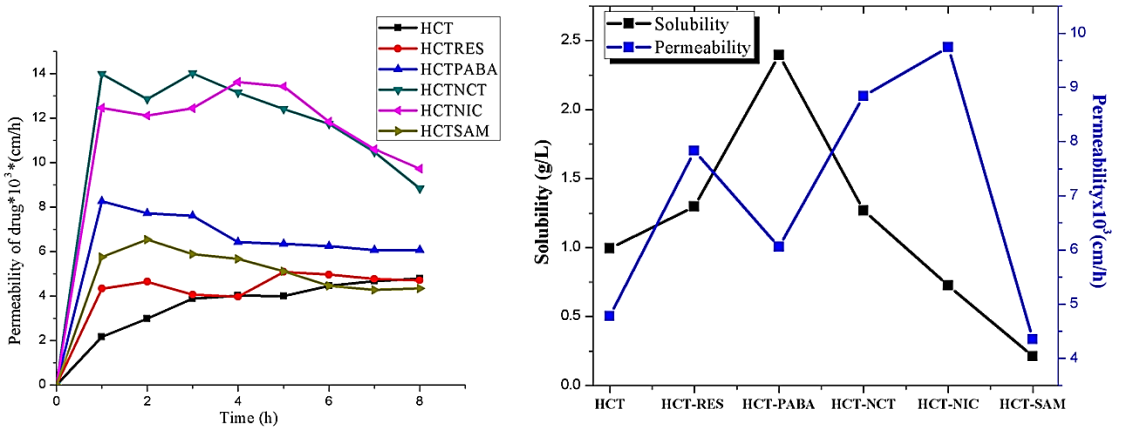


Figure 1.13 Dissolution profiles of ribavirin from and its cocrystals 1−3 in PBS (pH 6.8) demonstrate the reduced release of drug in cocrystals [113].

1.4.7.3 Permeability

Permeability through biological membranes is a crucial aspect of the absorption and delivery of drugs for better efficacy [114]. Based on the intestinal permeability and aqueous solubility drugs are classified into four categories. The drugs having extremely low solubility/permeability are classified as BCS class IV drugs. Different factors such as structural features, membrane-based efflux mechanisms etc. are responsible for poor permeability of a drug [114]. Low permeation of drug is avoidable as it causes substantial problems on absorption and release of a drug across the gastrointestinal membrane and thus the drug efficacy gets reduced. Currently, cocrystallization of poorly permeable drugs emerges as an effective means to boost up the permeation. Desiraju et al. demonstrated a cocrystallization strategy to improve the permeability of hydrochlorothiazide (HCT), a BCS class IV drug, via cocrystallizing with coformers like nicotinic acid (NIC), nicotinamide (NCT), 4-aminobenzoic acid (PABA), succinamide (SAM), and resorcinol (RES) [115]. Flux/ permeability of the cocrystals was studied by using a Franz diffusion cell. In almost all cases enhanced flux/permeability was observed except for the succinamide cocrystal and it is in the order HCT–NIC > HCT–NCT >HCT–PABA > HCT–RES > HCT > HCT–SAM. A trade-off between solubility and permeability was observed for the cocrystal as solubility increase is accompanied by a drop in permeability. Improved permeability of the cocrystals was attributed to the formation of sulfonamide–amide heterosynthon that exists between the API and the coformer.



(a) (b)

Figure 1.14 (a**)** Plots of permeability of the cocrystals with respect to time; (b) the permeability–solubility interplay correlation plot in cocrystals of hydrochlorothiazide [115].

In another study, Lu et al. demonstrated the in vitro skin permeation of acyclovir, an anti-HIV drug (ACV) and its maleate salt, fumaric acid and glutaric acid cocrystals [116]. Enhancement of both solubility and permeability of acyclovir were observed for cocrystals compared to ACV. The cumulative amount of drug permeation follow the order 0.0643 ($ACV_2/3H_2O$)> 0.0415 (maleic acid salt) < 0.1719 (fumaric acid cocrystal) < 0.2616 (glutaric acid cocrystal) mg/cm^3. It is significant that the acyclovir cocrystal with fumaric and glutaric acids demonstrates higher permeability over its maleate salt. The authors articulated that the improved permeability is due to the hydrophobic nature (larger log P) of the coformer. Similar improvement in membrane permeability and solubility of ethenzamide cocrystals considering hydroxybenzoic acids as coformers is attributed to the lipophilic nature of the coformers and is illustrated in Chapter 4.

1.4.7.4 Bioavailability

Bioavailability is well-defined as the amount and rate at which the drug or metabolite goes into a living being and reaches the site of action. Bioavailability is mainly determined by the properties of the dosage form [117]. Low oral bioavailability of APIs is a major challenge during the development of a new formulation. The overall bioavailability of a drug is subjected to its biopharmaceutical properties that include the aqueous solubility and permeability. Crystal engineering offers the potential route to design and synthesis of new pharmaceutical cocrystals to enhance aqueous solubility and

in this manner to improve the oral bioavailability. This tactic is specifically appropriate for those APIs that are included in the BCS class II category, which has a lack of ionisable functional sites for salt formation. Carbamazepine (CBZ) is an anticonvulsant drug with low water solubility, stability and poor dissolution rate. These inadequacies of CBZ were minimized in its cocrystal with sweetener saccharin (SAC). The 1:1 carbamazepine: saccharin cocrystal demonstrated improved physicochemical properties such as favourable dissolution rate and stability [118]. The cocrystal was administered orally to dogs and it was found that cocrystal attained better plasma concentrations than the drug CBZ. The cocrystal exhibited higher C_{max} (maximum drug concentration) and equivalent T_{max} (time to reach peak concentration) than the marketed formulations of CBZ, which include Tegretol XR and Carbatrol as shown in Figure 1.15. Hickey et al. explained this better bioavailability of CBZ on the basis of the improved solubility of cocrystal.

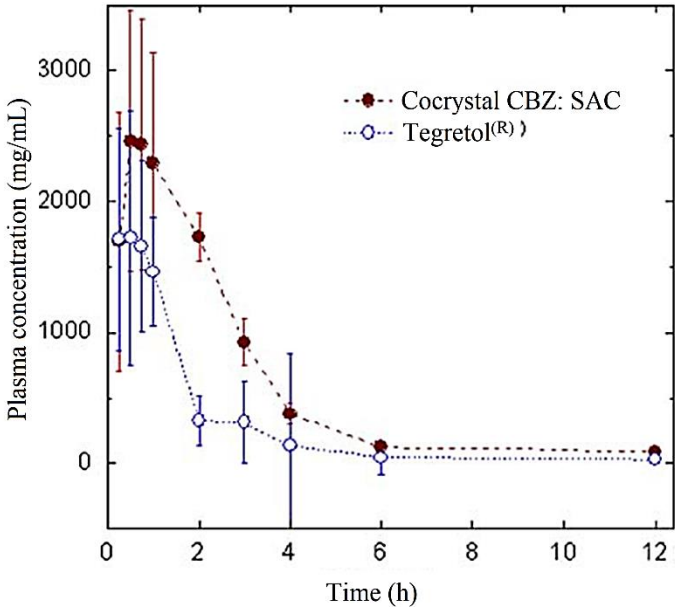
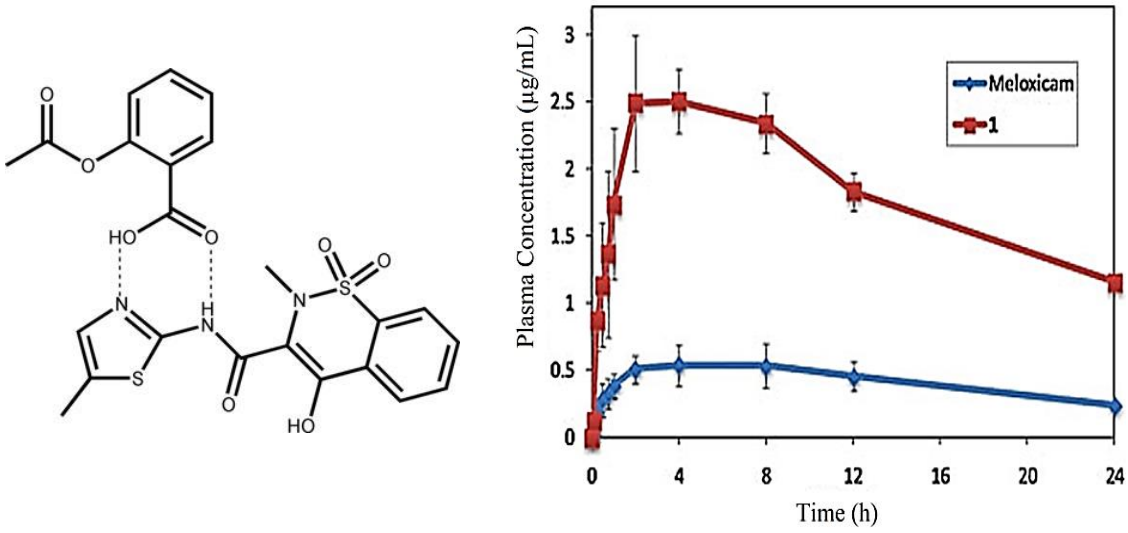


Figure 1.15 Average plasma time curves of carbamazepine concentrations (±SEM) from a cross-over experiment in fasted beagle dogs given oral doses of 200 mg of the active drug as Tegretol tablets and cocrystal [118].

Meloxicam is a nonsteroidal anti-inflammatory drug with very poor aqueous solubility (BCS class II). Cocrystals of it with a series of aliphatic and aromatic carboxylic acid derivatives were studied to modulate the in vitro solubility and pharmacokinetics in rats [119]. Majority of the cocrystals showed enhancement in intestinal absorption of meloxicam compared to pure API. The linear regression analysis demonstrated a robust

linear correlation between *in vitro* dissolution and mean serum concentration results in a majority of cocrystals at the identical time range. In another example, Cheney et al. demonstrated a coformer selection strategy to synthesise a drug-drug pharmaceutical cocrystal of meloxicam with desired physicochemical and pharmacokinetic properties. Aspirin was selected as coformer relying on the supramolecular synthon approach, combining with the prior information about meloxicam pharmacological and toxicological properties. The cocrystal exhibited superior kinetic solubility and it required approximately 12-fold lesser time to reach equivalent plasma concentration of 0.51 µg/mL in rats compared to the pure drug at an equivalent dose as shown in Figure 1.16.



(a) (b)

Figure 1.16 (a) Molecular structures of meloxicam and aspirin; (b) Plasma pharmacokinetics profiles over 24 h for cocrystal (1) and meloxicam from a 1mg/kg dose of meloxicam or its equivalent of cocrystal in rats [119].

In a recent study Corner *et al.* demonstrated a property prediction and pharmacokinetic evaluation of varied stoichiometry cocrystals of asthma drug zafirlukast with piperazine (1:1, 2:1 and 3:2:2 toluene) [120]. The cocrystals exhibited improved solubility and *in vivo* absorption behaviour in Wistar Han rats compared to the parent API. The *in vivo* experimental findings matched the expectation from *in vitro* investigation.

1.4.7.5 Mechanical Properties

Cocrystals are also instrumental in modulating the mechanical properties of drug molecules like tensile strength, compressibility, elasticity etc. These properties are important from the perspective of drug formulation, as they are related to bulk powder compaction or tablelability. The mechanical properties of cocrystals are found to be related to the crystal packing. Various researchers are systematically investigating the relationship between mechanical properties and crystal structure. For instance, Sun et al. validated how the presence of slip planes in the crystal structure is responsible for improved plasticity and tablelability of caffeine and methyl gallate cocrystal [121]. Similarly, due to the presence of slip planes, theophylline cocrystal with methyl gallate also exhibits better powder compaction [122]. In another example, Karki et al. demonstrated the improvement of tablelability of paracetamol (pca) polymorph **1** by introducing parallel extensive hydrogen bonding and π-π stacking layer in cocrystal with oxalic acid (oxa), caffeine (caf), theophylline (thp), phenazine (phe), and naphthalene (nap) [123]. The entire cocrystals exhibit improved tablelability than paracetamol form **1**. In another example, paracetamol cocrystal with trimethylglycine also exhibits improved tablelability. Therefore, a better understanding of the relationship between the crystal packing and mechanical properties is instrumental to resolve drug formulation difficulties.

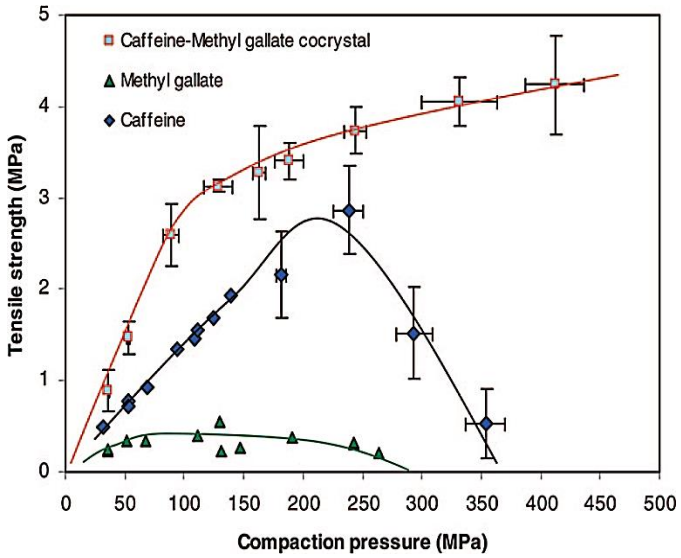


Figure 1.17 Comparisons of tablelability plot of caffeine, methyl gallate, and their 1:1 cocrystal shows improved tablelability for the cocrystal [121].

Sanphui et al. carried out a nanoindentation experiment to understand the mechanical property (hardness) of cocrystal and salt of voriconazole, an antifungal drug, a very soft material for tablelating and compaction [124]. The hydrochloric salt of voriconazole has maximum hardness attributed to the presence of strong ionic interactions and hydrogen bonds in the crystal structure as well as an absence of slip planes in the crystal lattice. Whereas, due to the presence of slip planes and weak interactions cocrystals become soft.

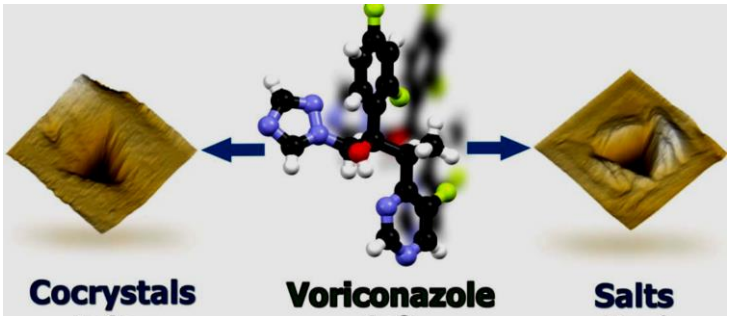


Figure 1.18 A pictorial comparison of softness–hardness of voriconazole cocrystal and salt [124].

1.4.7.6 Cocrystals of Pharmaceutical Interest

The recent development of cocrystal draws added interest from the pharmaceutical industries for better drug formulation. Additionally, new cocrystal has the ability to emerge as a contender for a new patent in drug formulation due to its novelty, efficacy, economic feasibility and easy synthetic procedure. There are reports on drug-drug cocrystals, nutraceutical cocrystals with improved properties in literature and in near future they may emerge as a viable alternative for traditional medicines. Recently, Sarma et al. published a review covering all the aspects of drug-drug cocrystals, drug-nutraceutical cocrystal [125]. The approval of the cocrystal drug ENTRESTO by FDA on July 7, 2015, a cocrystal of sacubitril and valsartan, which is a medication for certain types of chronic heart failure boost up further research on cocrystal [126,127]. Successively, Novartis has received approval for another drug ODOMZO, a cocrystal of sonidegib monophosphate and phosphoric acid from FDA for the treatment of basal cell carcinoma (skin cancer) [128]. On January 17, 2014 Pharmaceuticals and Medical Devices Agency of Japan (PMDA) approved ipragliflozin L-proline cocrystal, marketed as Suglat® developed by Astellas in collaboration with Kotobuki Pharmaceutical and

Merck Sharp & Dohme [129]. It is a sodium-glucose cotransporter 2 (SGLT2) inhibitor and used for the treatment of type 2 diabetes. In 2017, FDA approved another diabetes drug STEGLATRO™, a nutraceutical cocrystal of ertugliflozin and pyroglutamic acid. It is an oral sodium-glucose transporter 2 (SGLT2) inhibitors, manufactured by Pfizer and Merck [130]. An example of drug dug cocrystal E-58425 comprises of Tramadol and Celecoxib is undergoing in phase III clinical trial [131]. This cocrystal offers higher bioavailability for celecoxib and tramadol safety because of its lower dose. Depakote a leading marketed form of liquid drug valproic acid is a cocrystal of sodium valproate with liquid drug valproic acid [61]. In a recent review, Kavanagh et al. highlighted the discovery and market impact of pharmaceutical cocrystal [132].

1.5 Drug Polymorphism

Polymorphism is the existence of same chemical compound in more than one crystalline modification as defined by McCrone in 1965 [133]. In fact, about 90 % of organic compounds are known to exist in more than one solid form of which half can be polymorphic [133]. However, finding a new polymorph is difficult as stated by McCrone in 1965 "*the number of polymorphs of a given compound is proportional to the time and money spent on research on the compound*." The subject of drug polymorphism has received extensive academic and industrial attention since the reports of Aguiar and co-workers about the effect of the polymorphism on dissolution and bioavailability of chloramphenicol palmitate [134]. Polymorphism has significant importance in the pharmaceutical industry because polymorphs of the same drug molecule are legally classified as a different drug having different physicochemical properties which include manufacturability, stability, melting point, density, mechanical behaviour, solubility and bioavailability, etc. [45–47]. In the development of drugs, polymorphism influence the process at a various level which includes patent protection, polymorph identification and characterization, development and process control to achieve reliable crystallization outcomes. During drug formulation, selecting the appropriate polymorph i.e. lowest energy crystalline polymorph is important, as the discovery of new polymorphs of a drug could even threaten the commercial interest of a company and it can also be a patented material. The marketed formulation of 'ritonavir' an early example of a drug that inhibits the HIV-1 protease was forced to withdraw due to the discovery of stable form

(form II) with less dissolution profile which precipitated as crystals from the formulated ritonavir (form I) drug [135,136].

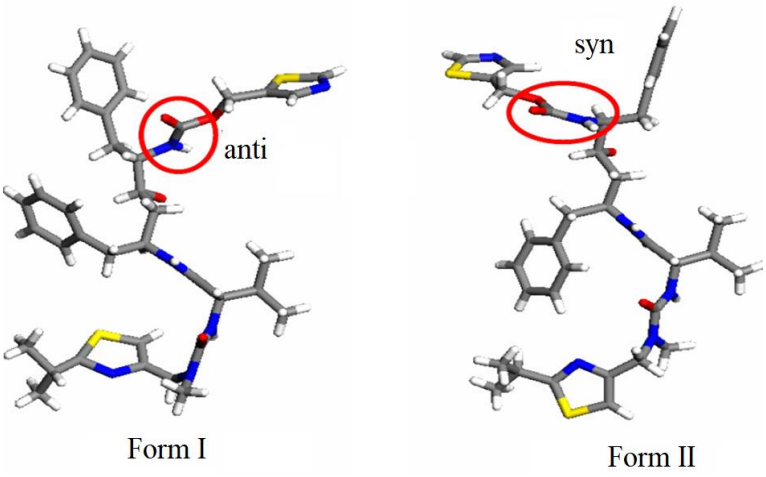
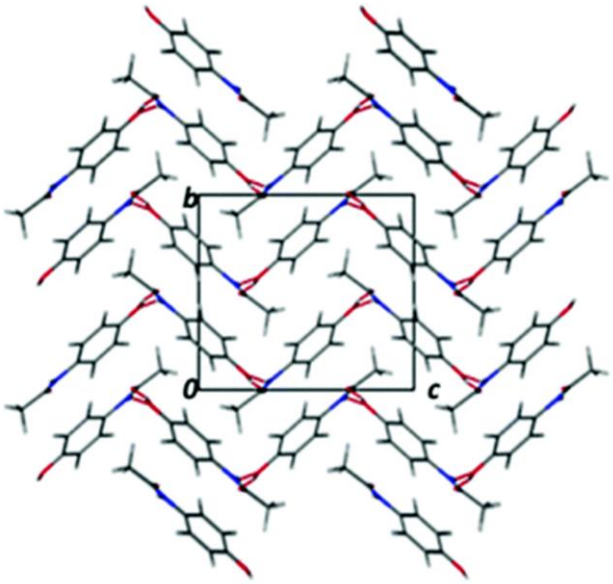
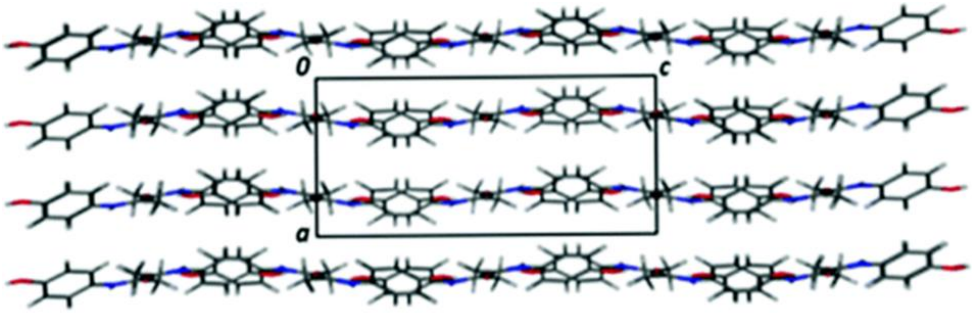


Figure 1.19 Conformational polymorphism that observed in ritonavir Form I and II [136].

Chemical stability difference of polymorphs has been reported for drugs like carbamazepine, indomethacin, furosemide etc. [137–139]. For instance, the photodegradation of carbamazepine form II has been reported as 5 times faster than form I and 1.5 times faster than form III [137]. Polymorphism can also affect the mechanical properties of drugs, thus impacting the manufacturability and physical characteristics of tablets. Crystal structures have a profound influence on the mechanical properties of a drug. Chun and co-worker demonstrated the impact of crystal structure on tabletability of sulfamerazine polymorphs [140]. In the case of paracetamol, a well-known analgesic drug, form I of the compound lacks slip planes in its crystal structure, which make it unsuitable for direct compression into tablets [141]. In contrast, form II of paracetamol contains slip planes in the crystal structure giving a layered packing, which provides processing benefits for this polymorphic form over form I (Figure 1.20).



Form I



Form II

Figure 1.20 Crystal packing diagram of two polymorphic forms of paracetamol. Due to the presence of a slip plane in the crystal structure, polymorphic form II displays better tablelability over form I [141].

These scenarios emphasize the need to screen for polymorphs in the pharmaceutics market. However, control of the crystallization of a high energy specific polymorph and its reproducibility is a challenging task. The understanding and control of the nucleation are extremely crucial for the crystallization process as it plays a decisive role in determining the crystal form, size, shape and eventually its properties. Numerous approaches such as anti-solvent techniques, melt-crystallization, sublimation etc. have been applied by researchers to control the polymorphic outcome; however, the underlying nucleation processes are poorly understood and difficult to control [142]. Nucleation is the first step of crystallization process from a solution, a liquid, or a vapour

in which small numbers of molecules, ions or atoms become arranged in a pattern characteristic of a crystalline solid creating a site upon which additional particles are deposited as the crystal grows [143]. In solution crystallization, nucleation plays a decisive role in determining the crystal structure and size distribution. Thus, there is scope to modify crystallization processes in order to understand and control nucleation with a view to polymorph control and the discovery of hard-to-nucleate solid forms. Introduction of specific functionality on templates on an active surface can act as seed/bed thereby controlling the nucleation process and leading to a single crystal of a desired or novel polymorph via controlled heterogeneous secondary nucleation.

In recent years the design and synthesis of low molecular weight organogels (LMWG) are gaining considerable attention from researchers owing to their applicability as a heterogeneous nucleation site for drug crystallization [144,145]. Gels are semi-solid type material composed of low concentrations (<15% more or less) of gelator molecules that, in the presence of the accurate solvent, self-assembled through different intermolecular interactions into an extensive mesh network preventing solvent flow as a result of surface tension [146]. Organogels are distinguished by their predominantly organic continuous phase and can then be further subdivided based on the nature of the gelator molecule: polymeric or low molecular weight organogelators (LMWGs). LMWGs, gelators which molecular mass is typically ≤3000 are composed of 3D networks of organic molecules, self-assembled through non-covalent interactions such as hydrogen bonding, π–π stacking and van der Waals interaction with the inclusion of solvent molecules [146,147]. Steed et al. demonstrated the use of supramolecular organogels for crystallizing of a range of drug substances such as carbamazepine, sparfloxacin, piroxicam, theophylline, caffeine, ibuprofen, acetaminophen (paracetamol), and indomethacin etc. [145]. Low molecular organogels are found to be effective in crystallizing hardly crystallize drug molecules, crystal habit modification, generation of new polymorphic phases etc. In Chapter **6** we have described a systematic drug mimetic gel phase crystallization approach to control the polymorphic outcome of drug molecules anticipating that gel surfaces will act as potential nucleation sites for drug crystallization.

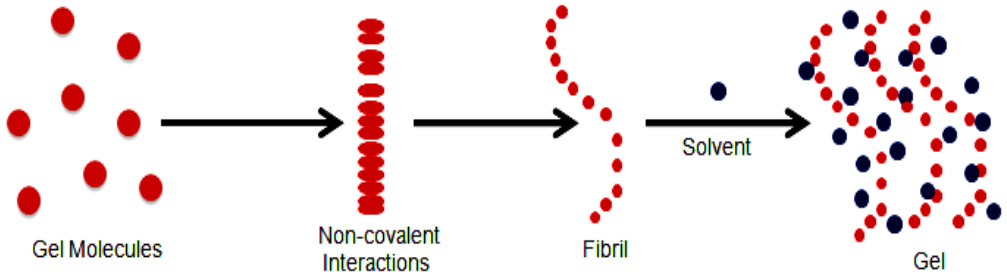


Figure 1.21 Pictorial representation of gel formation.

1.6 Summary

The subject crystal engineering provides a wide range of opportunity for the researchers to engineer various innovative solid-state drug formulations. With a greater understanding of the fundamentals of crystal engineering lays the potential for the development of a vast array of novel materials for a plethora of applications. These formulations can display tailored biopharmaceutical properties particularly with regard to solubility, processability and permeability and thereby bioavailability. The important role of various solid state forms such as polymorphs, salts, solvates and cocrystals in the pharmaceutical industry is of current research focus and is discussed in subsequent chapters. Improvement of different physiochemical properties such as aqueous solubility, hydration stability and poor dissolution rate of different APIs such as theophylline, propofol, ethenzamide, sulfathiazole, famotidine is address in this thesis by using cocrystal technology. In addition, use of drug mimetic organogels as crystallization media for controlling drug polymorph nucleation is also demonstrated.

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